Decision Summary

CMS was asked to reconsider Section 220.6 of the National Coverage Determinations Manual to end the prospective data collection requirements across all oncologic indications of FDG PET except for monitoring response to treatment. Section 220.6 of the NCD Manual establishes the requirement for prospective data collection for FDG PET used in the diagnosis, staging, restaging and monitoring response to treatment for brain, cervical, ovarian, pancreatic, small cell lung and testicular cancers, as well as for cancer indications not previously specified in Section 220.6 in its entirety.

We received public input indicating that the current coverage framework which required cancer-by-cancer consideration of diagnosis, staging, restaging and monitoring response to treatment should be replaced by a more omnibus consideration. Thus, we broadened the scope of this review through an announcement on our website and solicited additional public comment on the use of FDG PET imaging for solid tumors so that we could transparently consider this possibility. Therefore, we propose the following decision, which would replace sections 220.6.2, 220.6.3, 220.6.4, 220.6.5, 220.6.6, 220.6.7, 220.6.11, 220.6.12, 220.6.14 and 220.6.15 of the NCD Manual.

1. Framework
We propose a new coverage framework that would replace the four-part diagnosis, staging, restaging and monitoring response to treatment categories with a two-part framework that differentiates FDG PET imaging used to inform the initial treatment strategy from other uses related to guiding subsequent treatment strategies after the completion of initial treatment. We propose to make this change for all NCDs that address coverage of FDG PET for oncologic conditions.

2. Initial Treatment Strategy
CMS proposes that the evidence is adequate to determine that the results of FDG PET imaging are useful in determining the appropriate initial treatment strategy for beneficiaries with suspected solid tumors and thus improve health outcomes and are reasonable and necessary under §1862(a)(1)(A) of the Social Security Act.

Therefore, CMS will cover one FDG PET study for beneficiaries who have solid tumors that are biopsy proven or strongly suspected based on other diagnostic testing when the beneficiary's treating physician determines that the FDG PET study is needed to determine the location and/or extent of the tumor for the following therapeutic purposes related to the initial treatment strategy:

- To determine whether or not the beneficiary is an appropriate candidate for an invasive diagnostic or therapeutic procedure; or
- To determine the optimal anatomic location for an invasive procedure; or
- To determine the anatomic extent of tumor when the recommended anti-tumor treatment reasonably depends on the extent of the tumor.

As an exception to this decision:

a. CMS has reviewed evidence on the use of FDG PET imaging to determine initial antitumor treatment in patients with adenocarcinoma of the prostate. CMS proposes that the available evidence does not demonstrate that FDG PET imaging improves physician decision making in the determination of initial anti-tumor treatment strategy in Medicare beneficiaries who have adenocarcinoma of the prostate, does not improve health outcomes and is thus not reasonable and necessary under §1862(a)(1)(A) of the Social Security Act. Therefore we are proposing that FDG PET is nationally noncovered for this indication.

b. CMS did not review new evidence on the use of FDG PET imaging to determine initial antitumor treatment in breast cancer; thus we are not proposing any change to the current coverage policy for FDG PET in breast cancer. We will continue to cover FDG PET imaging for the initial treatment strategy for male and female breast cancer only when used in staging distant metastasis. FDG PET imaging for diagnosis and initial staging of axillary nodes will remain noncovered.

c. CMS did not review new evidence on the use of FDG PET imaging of regional lymph nodes in melanoma; thus we are not proposing any change to the current NCD for FDG PET in melanoma. CMS will continue noncoverage of FDG PET for the evaluation of regional lymph nodes in melanoma. Other uses to determine initial treatment strategy remain covered.

3. Subsequent Treatment Strategy

CMS reviewed evidence on the use of FDG PET in the subsequent treatment strategy for patients with tumor types other than breast, cervix, colorectal, esophagus, head and neck (non-CNS/thyroid), lymphoma, melanoma, non-small cell lung, and thyroid. For all other tumor types, CMS proposes that the available evidence is not adequate to determine that FDG PET imaging improves physician decision making in the determination of subsequent anti-tumor treatment strategy and thus does not improve health outcomes in Medicare beneficiaries and is not reasonable and necessary under §1862(a)(1)(A) of the Social Security Act. However, we propose that the available evidence is sufficient to determine that FDG PET imaging for subsequent anti-tumor treatment strategy is reasonable and necessary under §1862(a)(1)(E) through Coverage with Evidence Development/Coverage with Study Participation (CED/CSP)) of the Social Security Act.

Therefore, we will cover a subsequent FDG PET study for these tumor types when the beneficiary's treating physician determines that the FDG PET study is needed to inform the subsequent antitumor treatment strategy and the beneficiary is enrolled in, and the FDG PET provider is participating in, one of the following types of prospective clinical studies:

- A clinical trial of FDG PET that meets the requirements of Food and Drug Administration (FDA) category B investigational device exemption (42 CFR 405.201); or
- An FDG PET clinical study that is designed to collect additional information at the time of the scan to assist in patient management. Qualifying clinical studies must ensure that specific hypotheses are addressed; appropriate data elements are collected; hospitals and providers are qualified to provide the PET scan and interpret the results; participating hospitals and providers accurately report data on all enrolled patients not included in other qualifying trials through adequate auditing mechanisms; and all patient confidentiality, privacy, and other Federal laws must be followed.

The study must adhere to the following standards of scientific integrity and relevance to the Medicare population:

a. The principal purpose of the research study is to test whether a particular intervention potentially improves the participants' health outcomes.
b. The research study is well-supported by available scientific and medical information or it is intended to clarify or establish the health outcomes of interventions already in common clinical use.
c. The research study does not unjustifiably duplicate existing studies.
d. The research study design is appropriate to answer the research question being asked in the study.
e. The research study is sponsored by an organization or individual capable of executing the proposed study successfully.
f. The research study is in compliance with all applicable Federal regulations concerning the protection of human subjects found in the Code of Federal Regulations (CFR) at 45 CFR Part 46. If a study is regulated by the Food and Drug Administration (FDA), it also must be in compliance with 21 CFR Parts 50 and 56.
g. All aspects of the research study are conducted according to the appropriate standards of scientific integrity.
h. The research study has a written protocol that clearly addresses, or incorporates by reference, the Medicare standards.
i. The clinical research study is not designed to exclusively test toxicity or disease pathophysiology in healthy individuals. Trials of all medical technologies measuring therapeutic outcomes as one of the objectives meet this standard only if the disease or condition being studied is life-threatening as defined in 21 CFR § 312.81(a) and the patient has no other viable treatment options.
j. The clinical research study is registered on the www.ClinicalTrials.gov website by the principal sponsor/investigator prior to the enrollment of the first study subject.
k. The research study protocol specifies the method and timing of public release of all pre-specified outcomes to be measured including release of outcomes if outcomes are negative or study is terminated early. The results must be made public within 24 months of the end of data collection. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. However, a full report of the outcomes must be made public no later than three (3) years after the end of data collection.

l. The research study protocol must explicitly discuss subpopulations affected by the treatment under investigation, particularly traditionally underrepresented groups in clinical studies, how the inclusion and exclusion criteria affect enrollment of these populations, and a plan for the retention and reporting of said populations on the trial. If the inclusion and exclusion criteria are expected to have a negative effect on the recruitment or retention of underrepresented populations, the protocol must discuss why these criteria are necessary.

m. The research study protocol explicitly discusses how the results are or are not expected to be generalizable to the Medicare population to infer whether Medicare patients may benefit from the intervention. Separate discussions in the protocol may be necessary for populations eligible for Medicare due to age, disability or Medicaid eligibility.

Consistent with section 1142 of the Social Security Act (the Act), the Agency for Healthcare Research and Quality (AHRQ) supports clinical research studies that the Centers for Medicare and Medicaid Services (CMS) determines meet the above-listed standards and address the above-listed research questions.

For the nine tumor types listed below, we will continue to cover FDG PET for those indications currently covered under § 1862(a)(1)(A). We have not reviewed new evidence on these nine indications since they were reviewed in prior NCDs and we have not received public input suggesting coverage for these uses should be restricted. These include:

- Breast
- Cervix
- Colorectal
- Esophagus
- Head and Neck (non-CNS/thyroid)
- Lymphoma
- Melanoma
- Non-small cell lung
- Thyroid

We do propose transitioning the current framework—diagnosis, staging, restaging and monitoring—into the initial treatment and subsequent treatment strategy framework while maintaining current coverage.

See Appendix A for a chart summarizing the effect of these changes.

We are requesting public comments on this proposed determination pursuant to section 1862(1) of the Social Security Act. We are particularly interested in comments that include new evidence we have not reviewed here or in past considerations of this NCD.

We are specifically interested in comments on the following questions:

1. Should the current framework for evaluating the use of FDG PET imaging be modified as proposed?
2. Does the evidence support the broad expansion of coverage of FDG PET imaging to all solid tumors when determining initial treatment strategy?
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4. For breast cancer and melanoma that have noncoverage for initial treatment strategy, is there evidence that would support their removal from the list of exceptions to coverage for initial treatment strategy?
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Proposed Decision Memo

TO: Administrative File: CAG # 000181R1

FROM: Steve E. Phurrough, MD, MPA
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Shamiram Feinglass, MD, MPH
Medical Officer

Jeffrey C. Roche, MD, MPH
Medical Officer

SUBJECT: Proposed Decision Memorandum for Positron Emission Tomography (FDG) for Solid Tumors

DATE: January 6, 2009

I. Proposed Decision

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After considering the public comments and any additional evidence we will make a final determination and issue a final decision memorandum.

II. Background

Throughout this memorandum, we use the term FDG to refer to 2-deoxy-2-[F-18] fluoro-D-glucose, also known as F-18 fluorodeoxyglucose. We use the term FDG PET to refer to positron emission tomography or to a positron emission tomogram, depending on context. FDG PET refers to PET imaging utilizing FDG as the radioactive tracer. In the context of this document, the term FDG PET includes the use of combined or integrated positron emission tomography/computed tomography using FDG as the radioactive tracer (FDG PET/CT). We use the abbreviation MBq to denote megabecquerel, a unit of radioactivity in the International System of Units (SI). We use the abbreviation TNM to denote the dimensions of malignant tumor spread within a given patient, as defined by the American Joint Committee on Cancer and as used by National Cancer Institute, other clinical standards organizations and healthcare providers.

FDG PET is a minimally-invasive diagnostic imaging procedure used to evaluate glucose metabolism in normal tissue as well as in diseased tissues in conditions such as cancer, ischemic heart disease, and some neurologic disorders. FDG is an injected radioactive tracer substance (radionuclide) that gives off sub-atomic particles, known as positrons, as it decays. FDG PET uses a positron camera (tomograph) to measure the decay of radioisotopes such as FDG. The rate of FDG decay provides biochemical information on glucose metabolism in the tissue being studied. As malignancies can cause abnormalities of metabolism and blood flow, FDG PET evaluation may indicate the probable presence or absence of a malignancy based upon observed differences in biologic activity compared to adjacent tissues.

Other forms of diagnostic imaging technologies such as x-ray imaging, computed tomography (CT), and magnetic resonance imaging (MRI) supply information about the anatomic structure of suspected malignancies, primarily their size and location. However, clinical imaging of glucose metabolism within cells is unique to FDG PET technology. In many cases, the anatomical information provided by CT or MRI is most important in devising a treatment strategy. However, the metabolic information provided by FDG PET imaging may provide complementary information that is helpful in determining the initial treatment.

III. History of Medicare Coverage

CMS previously reviewed scientific literature and established coverage for many uses of FDG PET. A summary of currently covered FDG PET indications is in the following table. For each indication, specific coverage limitations are listed in the CMS NCD Manual, Section 220.6.

Currently covered FDG PET indications (FDG unless otherwise noted) are listed below.

Effective Date	Clinical Condition/Indication	Coverage
March 14, 1995	Myocardial perfusion	Rubidium-82 in coronary artery disease
January 1, 1998	Solitary pulmonary nodule	Characterization

Effective Date	Clinical Condition/Indication	Coverage
January 1, 1998	Non small cell lung cancer	Initial staging
July 1, 1999	Colorectal cancer	Suggested recurrence with rising CEA
July 1, 1999	Lymphoma	Staging and restaging as alternative to gallium scan
July 1, 1999	Melanoma	Recurrence prior to surgery as alternative to gallium scan
July 1, 2001	Non small cell lung cancer	Diagnosis, staging and restaging
July 1, 2001	Esophageal cancer	Diagnosis, staging and restaging
July 1, 2001	Colorectal cancer	Diagnosis, staging and restaging

Effective Date	Clinical Condition/Indication	Coverage
July 1, 2001	Lymphoma	Diagnosis, staging, and restaging
July 1, 2001	Melanoma	Diagnosis, staging and restaging. Non-covered for evaluating regional nodes.
July 1, 2001	Head and neck (excluding central nervous system and thyroid)	Diagnosis, staging and restaging
July 1, 2001	Refractory seizures	Pre-surgical evaluation
July 1, 2001 to September 1, 2002	Myocardial viability	Only following inconclusive SPECT
October 1, 2002	Myocardial viability	Primary or initial diagnosis
October 1, 2002	Breast cancer	Staging, restaging, response to treatment

Effective Date	Clinical Condition/Indication	Coverage
October 1, 2003	Myocardial perfusion	Ammonia N-13 in coronary artery disease
October 1, 2003	Thyroid cancer	Restaging of recurrent or residual disease
September 15, 2004	Alzheimer's disease and dementia	In CMS-approved clinical trial
January 28, 2005	Brain, cervical, ovarian, pancreatic, small cell lung and testicular cancers	Coverage with evidence development
January 28, 2005	All other cancers and indications not previously specified	Coverage with evidence development

A. Current Request

Medicare coverage policy regarding PET resides in Section 220.6 of the National Coverage Determination (NCD) Manual. The section and its subparts determine the general and specific conditions of Medicare coverage for various indications, including coverage where there was prospective data collection for FDG PET used in the diagnosis, staging, restaging and monitoring response to treatment for brain, cervical, ovarian, pancreatic, small cell lung and testicular cancers, as well as for cancer indications not previously specified in Section 220.6 in its entirety.

The requestors have asked CMS to reconsider Section 220.6 to end the prospective data collection requirements across all oncologic indications except for monitoring response to treatment.

B. Benefit Category

Medicare is a defined benefit program. An item or service must fall within a benefit category as a prerequisite to Medicare coverage §1812 (Scope of Part A); §1832 (Scope of Part B) and §1861(s) (Definition of Medical and Other Health Services) of the Act. FDG PET is considered to be within the following benefit category: other diagnostic tests §1861(s)(3). This may not be an exhaustive list of all applicable Medicare benefit categories for this item or service.

Medicare regulations at 42 CFR 410.32(a) state in part, that "…diagnostic tests must be ordered by the physician who is treating the beneficiary, that is, the physician who furnishes a consultation or treats a beneficiary for a specific medical problem and who uses the results in the management of the beneficiary's specific medical problem." Thus, except where other uses have been explicitly authorized by statute, Medicare does not cover diagnostic testing used for routine screening or surveillance.

IV. Timeline of Recent Activities

April 10, 2008	CMS accepts a formal request to reconsider Section 220.6 of the National Coverage Determinations Manual to end the prospective data collection requirements across all oncologic indications of FDG PET except for monitoring response to treatment. A tracking sheet was posted on the web site and the initial 30-day public comment period commenced.
May 10, 2008	The initial 30 day public comment period ended. Six hundred twenty-nine comments were received.
June 10, 2008	CMS will convene the Medicare Evidence Development and Coverage Advisory Committee on August 20, 2008. The panel will review the scientific evidence of the impact of FDG PET as part of a cancer management strategy to improve patient-centered outcomes. The panel will also consider data generated pursuant to prior national coverage determination to cover FDG PET for specified cancers when additional data are prospectively collected.
August 20, 2008	CMS convened the Medicare Evidence Development and Coverage Advisory Committee.
September 16, 2008	CMS broadens the scope of the NCA and an additional 30-day public comment commenced.
October 17, 2008	The additional 30-day public comment period ended. One hundred four comments were received.

V. FDA Status

The FDA approved the following uses for FDG F-18 in a Federal Register notice dated March 10, 2000 (Volume 65, Number 48) Notices. Pages 12999 -13010:

"The [FDA] Commissioner has concluded that FDG F 18 injection, when produced under the conditions specified in an approved application, can be found to be safe and effective in FDG PET imaging in patients with coronary artery disease CAD and left ventricular dysfunction, when used together with myocardial perfusion imaging, for the identification of left ventricular myocardium with residual glucose metabolism and reversible loss of systolic function, as discussed in section III.A.1 and III.A.2 of this document. The Commissioner also has concluded that FDG F 18 injection, when produced under the conditions specified in an approved application, can be found to be safe and effective in FDG PET imaging for assessment of abnormal glucose metabolism to assist in the evaluation of malignancy in patients with known or suspected abnormalities found by other testing modalities or in patients with an existing diagnosis of cancer, as discussed in section III.A.1 and III.A.3 of this document. In addition, manufacturers of FDG F 18 injection and sodium fluoride F 18 injection may rely on prior agency determinations of the safety and effectiveness of these drugs for certain epilepsy-related and bone imaging indications, respectively, in submitting either 505(b)(2) applications or amended new drug applications ANDAs for these drugs and indications."

VI. General Methodological Principles

When making national coverage determinations, CMS generally evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service falling within a benefit category is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. The critical appraisal of the evidence enables us to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for beneficiaries. An improved health outcome is one of several considerations in determining whether an item or service is reasonable and necessary.

A detailed account of the methodological principles of study design that the Agency generally uses to assess the relevant literature on a therapeutic or diagnostic item or service for specific conditions can be found in Appendix B.

Public commenters sometimes cite the published clinical evidence and provide CMS with useful information. Public comments that provide information based on unpublished evidence, such as the results of individual practitioners or patients, are less rigorous and, therefore, less useful for making a coverage determination. CMS uses the initial comment period to inform the public of its proposed decision. CMS responds in detail to the public comments that were received in response to the proposed decision when it issues the final decision memorandum.

VII. Evidence

A. Introduction

Below is a summary of the evidence we considered during our review. We will, of course, consider additional evidence submitted through the public comment period. CMS convened a Medicare Evidence Development and Coverage Advisory Committee (MEDCAC) meeting, and commissioned an external technology assessment (TA) from the Agency for Healthcare Research and Quality (AHRQ). The agency also conducted its own independent search and review of applicable clinical studies, professional society and other group/organization statements, evidence-based practice guidelines, and other relevant sources detailed below.

The Medicare regulations at 42 CFR 410.32(a) state in part, that "…diagnostic tests must be ordered by the physician who is treating the beneficiary, that is, the physician who furnishes a consultation or treats a beneficiary for a specific medical problem and who uses the results in the management of the beneficiary's specific medical problem." Thus, we looked for evidence demonstrating how the treating physician uses the result of an FDG PET imaging test to conduct the anticancer management in patients who are known to have solid tumors or who are reasonably suspected to have a high likelihood of cancer based on clinical findings and preliminary diagnostic testing.

The evidence base for many uses of FDG PET has expanded greatly since the first reconsideration of this decision in 2005. The evidence reviewed spanned many but not all cancer types; hence, this review will be organized based on how FDG PET may inform decisions regarding treatment strategy, both at the initial work-up stage and the subsequent work-up that might occur after a patient is initially treated. In many cases, prior NCDs have determined that FDG PET is nationally covered for specific indications. Given the large scope of the reconsideration we did not generally review evidence for indications that we believe to have been well supported by prior evidence reviews. We are of course open to reconsidering those coverage determinations if we become aware of evidence that they should be reconsidered. We are not considering here FDG PET for malignancies such as leukemia and myelodysplastic syndromes that are not classified as solid tumors.

B. Discussion of Evidence Reviewed

1. Questions

1. Is the evidence adequate to conclude that the results of an FDG PET scan will meaningfully alter the recommended initial treatment strategy for beneficiaries who have solid tumors or lesions suspected to be solid tumors?

2. Is the evidence adequate to conclude that the results of an FDG PET scan will meaningfully alter recommended subsequent treatment strategy in beneficiaries who have completed an initial treatment regimen for a solid tumor but who have signs or symptoms of tumor spread or recurrence?

3. Is the evidence adequate to conclude that the results of an FDG PET scan will meaningfully alter recommended subsequent treatment strategy in beneficiaries who have completed an initial treatment regimen for a solid tumor and who have no signs or symptoms of tumor spread or recurrence?

We have, regarding subsequent treatment strategies, separately considered patients who have signs or symptoms of recurrence from those who do not. We believe that a treating physician's approach may reasonably differ in these situations, possibly being more aggressive in a patient who is more acutely distressed and whose tumor has clearly not responded to the initial treatment strategy. Question 3 is posed in the context of a patient who has a known diagnosis of a solid tumor and in whom his treating physician is still actively managing the treatment of the solid tumor. We are not considering the use of PET as a screening test rather than as a diagnostic test.

2. External Technology Assessments

CMS did request an external technology assessment (TA) on this issue from the Agency for Healthcare Research and Quality (AHRQ). This TA was completed prior to our expansion of the scope of this review. Nonetheless we believe that it is relevant to our broader consideration of this topic.

The TA on FDG PET, with or without computerized tomography (FDG PET/CT)) scanning, was undertaken during 2008 by the University of Alberta Evidence-based Practice Center (UA-EPC) under contract from AHRQ. The UA-EPC reviewed and synthesized the evidence on the use of FDG PET in the assessment and treatment of nine types of cancer in the situations of diagnosis, staging, re-staging, and monitoring response to treatment.

In conducting this TA, the UA-EPC researchers focused on the following questions:

Q1. How does the diagnostic test performance of FDG PET compare to conventional imaging modalities (for example, CT or magnetic resonance imaging (MRI)) or other diagnostic procedures (e.g., biopsy, serum tumor markers) in the following situations?:
1) Diagnosis
2) Staging
3) Restaging
4) Monitoring response to treatment

Q2. What is the magnitude of the impact of FDG PET on physician decision making regarding approaches to diagnosis and management in the following situations?
1) Diagnosis
2) Staging
3) Restaging
4) Monitoring response to treatment

Q3. What is the impact of FDG PET as part of a management strategy to improve patient-centered outcomes? What is the ability of FDG PET to improve patient-centered outcomes when used as a diagnostic test to identify patients suitable for a particular treatment?

Q4. What is the cost-effectiveness of FDG PET with respect to the following clinical situations?
1) Diagnosis
2) Staging
3) Restaging
4) Monitoring response to treatment

The researchers noted that the TA did not focus on evidence concerning technical evaluation of imaging quality. Instead, the questions in this TA concentrated on studies evaluating FDG PET as related to Levels 2 – 6 of the Fryback and Thornbury model of technology assessment; that is, on diagnostic accuracy efficacy (Q1), diagnostic thinking efficacy (Q2), therapeutic efficacy, patient outcome efficacy (Q3), and societal efficacy (Q4).

In summary, the UA-EPC researchers found that:

- The strongest evidence for diagnostic accuracy of FDG PET or FDG PET/CT was for staging locally advanced cervical cancer and detection and restaging of recurrent disease, detection of ovarian cancer recurrences following treatment, and diagnosis and initial staging of pancreatic cancer.
- The UA-EPC researchers suggested that further research would be required to demonstrate the impact on patient management or value in the diagnostic or therapeutic process.
- For bladder, kidney, prostate, SCLC, and testicular cancers, current evidence about the effect of FDG PET on treatment and outcome was inconclusive. The UA-EPC researchers suggested that more study would be needed.

CMS reviewers examined the methodology and results of the TA and agreed with the UA-EPC findings as to the presence and strength of effects, which were felt to be supported by the selected articles included. CMS reviewers also found that in general, the conclusions of this TA were consistent with findings of an internal evidence review separately conducted by CMS staff.

3. Internal technology assessment

The reviewed evidence was gathered from articles submitted by the requestor and a literature search of the PubMed database.

Literature search methods

CMS performed an extensive literature search on April 17, 2008 utilizing PubMed for search terms "FDG PET and cancer". The search was limited to articles published in the last 5 years, humans, clinical trial, English, and age $\geq$ 65. We have also reviewed additional evidence that has come to light since that time which has been provided by the requestors, other members of the public, or through our own surveillance of the relevant medical literature. We are aware of more research in progress and we anticipate reviewing additional evidence that may become available to inform our final decision.

For clarity, we are sequentially addressing each question separately below.

1. Is the evidence adequate to conclude that the results of an FDG PET scan will meaningfully alter the recommended initial treatment strategy for beneficiaries who have solid tumors or lesions suspected to be solid tumors?

Below is a summary of the methodologically stronger evidence that was used to answer this question. Please see the evidence tables (Appendix C) for all evidence reviewed and referenced, including methodologically less rigorous evidence that was assigned lesser weight.

Bastiaannet E, et al. 2006
This is a retrospective review of 257 subjects with melanoma. FDG PET was evaluated for its impact on treatment strategy. The investigators reviewed 257 medical records and treatment plans before and after FDG PET. Examples of treatment changes made include decreased surgical intensity or a change to palliative care, changing from surgery to no surgery, and changing from no-treatment to systematic drug treatment. See the table below for details. The authors conclude that the information provided by FDG PET is important for surgical planning.

Comparison of treatment intended before FDG PET and actual treatment given

Intended treatment		Treatment performed								
		Surgery	Systemic treatment	Radiotherapy	No treatment	Surgery and systemic treatment	Surgery and radiotherapy	Systemic treatment and radiotherapy	Not clear	Total Changed (%)
Surgery	172	155	9	1	6			1		17 (10)
Systemic treatment	13	2	9		1			1		4 (30.7)
Radiotherapy	6		1	3	1			1		3 (50)
No treatment	56	3	5	2	45			1		11 (19.6)
Surgery and systemic treatment	1					1				1(0)
	3			1			2			1 (66.7)

Intended treatment		Treatment performed								
		Surgery	Systemic treatment	Radiotherapy	No treatment	Surgery and systemic treatment	Surgery and radiotherapy	Systemic treatment and radiotherapy	Not clear	Total Changed (%)
Surgery and radiotherapy										
Not clear	6			1	3				2	4 (66.7)

Pepe G, et al. 2005
This was a prospective case series of 75 subjects aged 33-82 with a diagnosis of a pulmonary lesion. Subjects were evaluated to see how FDG PET findings might alter treatment strategy. A questionnaire was sent to referring physicians before and after FDG PET results. Changes in patient management after FDG PET imaging occurred in 34 (45%) cases, with the most relevant variation occurring after FDG PET related to the surgical treatment strategy (see table below). Authors concluded that FDG PET was useful for altering treatment strategy, especially as relates to surgical strategy.

Results of treatment Strategy Changes pre- and post-FDG PET

	Pre-FDG PET	Post-FDG PET	% Change
Further Diagnostic work -up needed	44	27	38.6%

	Pre-FDG PET	Post-FDG PET	% Change
Surgery	9	28	211%
Wait & See	5	3	40%
Medical Therapy	17	17	No change

Castellucci P, et al. 2007

This prospective case series enrolled fifty consecutive female subjects, each of whom had a pelvic lesion suspicious for malignancy, had undergone transvaginal ultrasound and had elevated levels of CA-125. Subjects' ages were between 23 and 89 years, with a mean age of 64 years. Histopathologic findings at surgery were the comparison standard. The criterion for malignancy on FDG PET/CT was a maximum standardized uptake value (SUV_{max}) exceeding 3.0. Duplicate FDG PET/CT interpretations were performed by two experienced nuclear medicine physicians blinded to clinical and other diagnostic data. In FDG PET/CT scans of the 32 subjects with malignant lesions of the ovary, 28 had a SUV_{max} ranging from of 3.1 to– 125.7 and were considered to have malignant disease. FDG PET/CT studies of the other 4 subjects showed an SUV_{max} less than 3.0, while histopathology identified two serous papillary adenocarcinomas with microinvasion and two borderline mucinous adenocarcinomas in these four subjects. In comparison to transvaginal ultrasound (TVUS), FDG PET/CT showed greater specificity, positive predictive value, and accuracy. In addition, this study also examined the performance of FDG PET/CT compared to CT alone for staging. For more advanced tumors (Stages III and IV), FDG PET/CT was better at staging than CT alone, correctly staging 15/18 subjects with Stage III and IV disease, as compared to correct CT staging of 9/18 subjects. However, FDG PET was falsely negative in 4/11 subjects with stage I disease. The authors concluded that FDG PET/CT was useful for initial treatment strategy and could change patient management.

Connell CA, et al. 2007

Based on a prospective case series of 76 subjects, this study examined the pre- and post-treatment impact of FDG PET on patient management decisions in subjects with primary head and neck squamous cell cancer. Subjects' ages at diagnosis ranged from 21-83 years, with a median of 59 years. Thirty-five of seventy-six subjects underwent a staging FDG PET/CT scan, resulting in a change in TNM staging in 12/35 (34%). Two of these 12 had disease downstaged; 10/12 subjects had disease upstaged. These changes in stage had impacts on radiotherapy technique and dose planning. Seven subjects with negative neck node scans avoided futile neck dissections. One with persistent FDG-avid disease in the nasal cavity underwent earlier salvage surgery and two with suspected residual disease avoided systemic chemotherapy or biopsy. Finally, Kaplan-Meier survival analysis showed a significant difference in disease-free ($p = 0.046$) and overall ($p = 0.037$) survival based on FDG PET/CT assessment of a complete metabolic response, with a maximum clinical follow-up of as much as 45 months.

The authors concluded that FDG PET/CT imaging contributed to initial treatment strategy planning in patients with primary head and neck squamous cell cancer and suggested that the high FDG PET negative predictive value identified subjects in whom observation rather than surgical intervention would be appropriate and safe.

Hillner BE, et al. 2008

This prospective questionnaire-based case series of 22,976 subjects was undertaken in response to the 2005 FDG PET/CT for cancer NCD and resulted in the development and implementation of the National Oncologic FDG PET Registry (NOPR), which was designed to meet coverage requirements and to assess how FDG PET/CT affects care decisions. This questionnaire collected data from referring physicians on intended patient management before and after FDG PET/CT. The cohort included data on 22,975 patient studies (83.7% FDG PET/CT) from 1,178 centers. Prostatic, pancreatic and ovarian cancers represented in aggregate approximately 30% of cases. When intended management was classified as either treatment or nontreatment, the post-FDG PET plan was three-fold more likely to lead to treatment than nontreatment (28.3% v 8.2%; odds ratio 3.4; 95% CI, 3.2 to 3.6). Overall, physicians changed their intended management in 36.5% (95% CI, 35.9 to 37.2) of cases after FDG PET/CT. Authors conclude that physicians often change their intended management based on FDG PET/CT scan results across the full spectrum of its potential uses.

Meyers BF, et al. 2007

This prospective multi-institutional trial of 189 subjects, a re-analysis of an American College of Surgeons Oncology Group trial, examined whether FDG PET scan for staging of esophageal carcinoma identifies metastatic disease and avoids esophagectomy in subjects who are surgical candidates after routine staging. Of the 262 subjects registered, 199 were considered eligible and of these, 189 subjects were evaluated. Ineligible subjects were those considered unresectable by routine staging procedures, those without cancer, those whose care violated FDG PET protocols or those with claustrophobia or other reasons. FDG PET indicated involvement of local lymph nodes in a greater proportion of study participants than did CT (58 (30.7%) with local lymph node involvement by FDG PET versus 23 (12.2%) by CT). Also, FDG PET detected involvement of distant organs in 33 subjects (17.5%) as opposed to none (0%) by CT. In 7/189 subjects, FDG PET findings of metastatic disease were not confirmed. The authors commented on the added burden of investigating the FDG PET false positives, including complications of procedures that resulted in serious outcomes for the participants such as unnecessary adrenalectomy or surgical site infection. However, FDG PET detection of metastases to distant lymph nodes or organs was a major reason for a decision to avoid surgery in 4.8% of surgical candidates.

Authors concluded that FDG PET after standard clinical staging for esophageal carcinoma identified previously undetected metastases in distant organs in 4.8% of subjects before resection. FDG PET evidence of metastases to distant lymph nodes or organs and of metastases to regional lymph nodes led to definitive nonsurgical or induction therapy in additional subjects.

Ng SH, et al. 2004
This prospective case series of 37 subjects was examined to assess the usefulness of FDG PET in subjects whose MRI findings during periodic (every 6 months during first two years after radio- or radio-chemotherapy) surveillance for nasopharyngeal carcinoma (NPC) were questionable for recurrence. The average age of the 37 subjects was 47.2 years, with 13 females and 24 males. Questionable MRI findings were those beyond expected morphologic findings after radio-therapy, either equivocal or suggesting residual or recurrent NPC. FDG PET was performed within two weeks of the MRI study and interpreted by three nuclear medicine physicians who were unaware of the MRI findings. Lesions were examined either by histopathology or by clinical follow-up of at least 6 months. Overall performance using either histopathology or clinical follow-up as the gold standard in these 37 subjects with questionable MRI findings for recurrence included:

Scan Type:	Sensitivity	Specificity	Accuracy	PPV	NPV
FDG PET	89.5%	55.6%	72.9%	68.0%	83.3%

In six subjects with false-positive FDG PET findings, inflammation was noted at the primary tumor site on histopathologic examination. In one patient, a false negative FDG PET finding at the primary site was attributed to intramucosal residual tumor by histopathology. FDG PET findings in regional lymph nodes were considered false-positives in three subjects, with inflammatory activity on histopathology in two subjects or regression on clinical follow-up in one patient. One false-negative FDG PET finding was attributed to a small focus of metastatic involvement in a 0.5 cm diameter lymph node. Of eight subjects found positive by FDG PET for distant metastases, five were confirmed by histopathology or by progression in subsequent images, and three false positive FDG PET findings at distant sites were attributed to inflammation by either biopsy or resolution by imaging or clinical follow-up. Twenty-nine subjects were negative for distant metastases by FDG PET. However, in the discussion section, the authors comment that in one patient, small foci of lung metastases, visible on CT and enlarging in diameter on repeat CT two months later, were missed by FDG PET (although a larger perihilar focus was detected).

The authors concluded that significant additional information was provided by FDG PET findings for 18/37 participants with questionable MRI findings, including unexpected small metastases in lymph nodes in three, distant metastases in five, and exclusion of recurrence in 10 subjects.

Risum S, et al. 2007

This prospective case series of 97 subjects examined the use of combined FDG PET/CT in detecting malignancy in subjects with no cancer history but with a pelvic mass (and therefore suspected primary ovarian carcinoma). One-hundred-one subjects referred for surgery from primary hospitals for suspected ovarian cancer were enrolled. Comparisons were based on 97 subjects for whom histopathologic studies were available (four subjects decided not to undergo surgery based on benign FDG PET/CT findings). The median patient age was 60 years. Risk for malignancy was estimated from ultrasound examination findings and elevated CA-125 antigen levels (median 784 U/mL, range 22-9665 U/mL). FDG PET/CT findings were compared with those of histopathologic studies of the pelvic masses for malignant and for borderline/benign lesions. Sensitivity and specificity for FDG PET/CT in diagnosing malignancy in a pelvic mass were, respectively, 100% (57/57) and 92.5% (37/40) ($p < 0.00005$). In several subjects, distant (inguinal and supraclavicular) lymph node or organ (spleen, lung) ovarian tumor metastases were detected by FDG PET/CT and confirmed by histopathology (and, in two subjects, metastases were found by FDG PET/CT from unsuspected primary malignancy elsewhere). Other subjects with FDG PET/CT evidence of abnormally increased metabolic activity that might have indicated metastatic disease were investigated in only one of sixteen. False positive FDG PET/CT results were noted in three subjects with benign pelvic masses (fibroma, leiomyoma and endometriosis by histopathology).

Authors concluded that combined FDG PET/CT demonstrates high diagnostic value in identifying ovarian cancer. Authors suggest FDG PET/CT as the image modality of choice when ultrasound shows a pelvic tumor and additional information prior to surgery is needed.

Schmidt GP, et al. 2005

This prospective case series of 41 examined the accuracy of staging MRI vs. FDG PET/CT. Test interpreters were blinded and solid tumors in various organs were evaluated lung, liver, bone, soft tissue, CNS. The authors found that FDG PET/CT detects tumors as well or better than MRI, was superior for lymph node staging, and was helpful in guiding biopsy and avoiding unnecessary biopsy. For lymph node detection, FDG PET/CT was 98% sensitive and 83% specific. Authors conclude that by using FDG PET/CT, "fruitless diagnostics, which burden the patient and can occur in a multimodality approach, could be avoided." However, the authors caution that MRI was superior to FDG PET for identifying distant metastases.

Suzuki, et al. 2007

This study of a prospective case series of 30 subjects with pelvic tumors addressed the value of FDG PET imaging for initial treatment strategy planning. Imaging findings before surgery were studied in subjects with biopsy-proven endometrial cancer, who underwent FDG PET, whole-body CT, and pelvic MRI within 2 weeks of surgery. The subjects' ages ranged from 27 to 73 years, with a mean of 55 years. Twenty-six of thirty subjects underwent retroperitoneal lymph node dissections; two had peritoneal dissemination of tumor. FDG PET was slightly more sensitive than CT/MRI for detection of extra-uterine metastases in other organs (5/6 (83%) vs. 4/6 (67%)), while both types of scans were equally specific for such lesions (both 24/24 (100%)). However, although FDG PET was less likely than CT/MRI to detect the rare, small (0.1 – 0.6 cm) pelvic lymph node metastases identified by histopathology in 5/26 subjects who underwent lymph node dissection, the difference was not statistically significant.

The authors conclude that negative FDG PET results should not be used to justify deferring surgical examination of regional lymph nodes.

Turkmen, et al. 2007

In this prospective study of the value of FDG PET in initial treatment strategy planning, pre-operative assessment of previously untreated non-small cell lung cancer (NSCLC) in 59 participants (47 men, 12 women) included FDG PET scans in addition to CT, with either thoracotomy for cure or lymph node biopsy for histopathologic staging. The median of the subjects' ages was 52 years, with ages of participants ranging from 44 – 83 years. For lymph node staging, FDG PET and CT performance characteristics were calculated separately for: a) patients with either no lymph nodes involved, or involvement limited to bronchopulmonary or hilar lymph nodes in the same lung; or b) patients limited to metastases of lymph nodes in the same side of the chest (including the mediastinum) but without lymph node involvement in the contralateral mediastinum or in the supraclavicular or scalene lymph nodes. These calculations are shown in parts a) and b) of the following table:

Table: FDG PET and CT performance characteristics:

a) Local or no lymph node involvement

Scan Type:	Sensitivity	Specificity	Accuracy	PPV	NPV
CT	66%	43%	58%	68%	43%
FDG PET	79%	76%	78%	86%	76%

b) Ipsilateral intrathoracic lymph node involvement

Scan Type:	Sensitivity	Specificity	Accuracy	PPV	NPV
CT	43%	66%	54%	41%	66%
FDG PET	76%	79%	80%	67%	83%

The authors concluded that an FDG PET scan significantly improves diagnostic accuracy of lymph node involvement by tumor as compared with CT ($p < 0.01$). False positive studies on FDG PET images were mostly attributable to lymph node foci of granulomatous diseases of various types (e.g., pulmonary tuberculosis, silicosis), which the authors commented to be higher than expected among the study population.

The authors concluded that FDG PET was of value for initial treatment strategy planning in patients with non-small cell lung cancers. However, in light of a false-negative rate exceeding 10% for mediastinal node involvement, with 20% of participants under-staged by FDG PET, the authors emphasized the importance of mediastinoscopy in FDG PET-negative patients for more accurate staging.

2. *Is the evidence adequate to conclude that the results of a FDG PET scan will meaningfully alter recommended subsequent treatment strategy in beneficiaries who have completed an initial treatment regimen for a solid tumor but who have signs or symptoms of tumor spread or recurrence?*

Connell CA, et al. 2007

Discussed above, this prospective case series of 35 subjects also addressed the impact of FDG PET on subsequent treatment strategy. FDG PET was performed in 32/35 subjects to assess response to therapy within a median of 3.2 months post-treatment (range 1.4 – 6.4 months). The FDG PET results were compared with ordinary radiologic assessments of treatment response done within 3 days of the FDG PET scan. Locoregional response of malignancy in 30 subjects changed due to FDG PET results in 13/30 (43%) of subjects. The authors concluded that the clinical impact was high for 11/30 subjects studied: 7 avoided unnecessary neck dissections, 1 with distant metastatic disease avoided futile salvage surgery, 1 with FDG-nonavid residual disease avoided systemic chemotherapy, 1 with non-avid disease in the tonsils avoided examination under anesthesia, and 1 with FDG-avid disease in the nasal cavity underwent salvage surgery.

Chung, et al. 2007

This prospective case series of 77 subjects was studied to evaluate the accuracy of integrated FDG PET/CT for detection of suspected recurrent ovarian carcinoma after treatment, using clinical or histopathologic findings as the reference standard. Seventy-seven women (median age, 51 years, range 21-80 years) with ovarian carcinoma treated with primary cytoreductive surgery followed by platinum-based combination chemotherapy were included. FDG PET/CT was performed for suspected recurrence. In all subjects, imaging findings were compared with results of histopathologic examination after surgical exploration or clinical follow-up to determine the diagnostic accuracy of FDG PET/CT in the evaluation of disease status. A high level of agreement was found between FDG PET/CT and histopathologic or clinical analyses ($\kappa = 0.894$). The overall sensitivity, specificity, accuracy, positive predictive value (PPV) and negative predictive value (NPV) of FDG PET/CT were 93.3%, 96.9%, 94.8%, 97.7% and 91.2%, respectively. FDG PET/CT modified the diagnostic or treatment plan in 19 (24.7%) subjects by leading to the use of previously unplanned therapeutic procedures in 11 (57.9%) subjects and the avoidance of previously planned diagnostic procedures in eight (42.1%).

The authors concluded that FDG PET/CT is sensitive for detecting recurrent ovarian cancer and aids treatment planning.

Kim S, et al. 2004

This retrospective case series of 55 women compared the prognostic value of FDG PET with that of second-look laparotomy (SLL) to detect recurrences in subjects with advanced ovarian cancer following surgery and chemotherapy. Of the 55 enrolled subjects, 30 underwent SLL, while 25 had FDG PET without SLL. Subjects had a mean age of 49.2 years, ranging from 25-78 years. All had histopathologically proven ovarian cancer. Prognostic value was based on retrospective medical record review. Recurrence was identified in 37 of the 55 subjects; 17 in the FDG PET group and 20 in the SLL group. Recurrent disease was confirmed by histopathology or cytology in 16/37 subjects and by physical exam, MRI, ultrasound, or CA-125 in 21/37 subjects. Diagnostic performance indices for recurrence identification by FDG PET were as follows:

	Sensitivity	Specificity	Accuracy	PPV	NPV
FDG PET	82%	88%	84%	70%	84%

Progression-free intervals (PFI) were not significantly different between the two groups: an average PFI of 28.8 months in the FDG PET group and 30.6 months in the SLL group ($p = 0.29$). The average disease-free intervals were also not significantly different between the FDG PET group (40.5 months) and the SLL group (48.6 months) ($p = 0.12$), or the positive FDG PET group and the positive SLL group (23.7 months and 26.2 months, respectively). The authors concluded that FDG PET could be used to substitute for SLL in subjects with ovarian cancer.

Mirallié E, et al. 2007

In this prospective multi-institutional study, the value of FDG PET was examined for subsequent treatment strategy planning in 45 patients with FDG PET findings indicating recurrences of differentiated thyroid cancer (DTC). The group included 31 males and 14 females. Subjects' ages ranged from 14-80 years, with a mean age of 55 years. All subjects had undergone total thyroidectomy and postoperative residual thyroid ablation with ^{131}I. All subjects had postoperative elevation of thyroglobulin levels, increased TSH, normal values of anti-thyroglobulin antibody, and negative whole-body ^{131}I scans. The study's findings are summarized in the following table.

FDG PET finding for recurrent DTC (# of patients)	Recurrence confirmed by histopathology	Recurrence confirmed on clinical follow-up with tissue confirmation	Recurrence not confirmed by any method
Positive (31)	24	0	7
Negative (14)	n/a	14	n/a

Histopathologic findings in those seven subjects with false-positive FDG PET results included: two patients with second primary tumors (one of lung, one of uterus); one patient with inflammation; and four patients with normal lymph nodes.

The study also assessed FDG PET performance characteristics for detecting recurrence. (In the absence of any true negative FDG PET studies for recurrence indicated in this article, specificity and negative predictive value were not assessed.)

	Sensitivity	Accuracy	PPV
FDG PET	63%	53%	77%

FDG findings also affected subsequent treatment strategy planning in 23 subjects:

FDG PET Finding	Outcome	Subjects:
Disseminated disease	Change from surgical to chemo - or radiation therapy	8
No abnormal focus	Change from surgical to chemo - or radiation therapy	14
Focal increase of activity near a prosthesis	No further diagnostic effort (observation only)	1

In a separate subgroup of 20 subjects, FDG PET findings localized recurrences in the neck, mediastinum, and/or lung. In 17/20 subjects, FDG PET showed from one to five foci in the lateral or central neck in each subject. In the other three subjects, FDG PET images showed: one lung focus in one; foci in both lung and neck in another; and foci in both lung and mediastinum in the third. Nineteen of these 20 subjects underwent resection. Histopathology confirmed lung metastasis in one patient; found no positive neck lymph nodes in three other patients; and detected from 1-6 lymph nodes positive for malignancy in the remaining 15. (One of the 20 subjects with FDG PET evidence of local recurrence did not undergo surgery.)

The authors concluded that, as a result of FDG PET findings, some subjects received curative secondary resection. In addition, surgery was avoided in eight subjects with disseminated disease.

Pepe G, et al. (2005)
Discussed above, this prospective case series contained a subset (n = 20) of subjects in which they were monitoring treatments. The resulting management changes were mostly to surgery, which was either curative or palliative. The authors conclude that this study suggests a benefit for FDG PET scans for monitoring response to treatment and further studies are needed to confirm this result.

Votrubova J, et al. 2006
The findings in this prospective case series were examined to assess the value of integrated FDG PET/CT in detecting recurrences of colorectal cancer after colonic resection. The 84 study participants included 54 men and 30 women with suspected recurrence of colorectal cancer following initial surgical resection. The mean age was 64 years (age range 41-78 years). FDG PET/CT was performed no earlier than one month after colorectal surgery. Forty-five of eighty-four participants demonstrated recurrence either by histopathology or by clinical follow-up. FDG PET/CT correctly detected recurrence in 40/45 and was correctly negative in 27/39 patients without recurrence. Overall performance characteristics of FDG PET/CT for detecting recurrence among participants were summarized as follows using data from the article.

	Sensitivity	Specificity	Accuracy	PPV	NPV
FDG PET/CT	89%	69%	80%	77%	84%

The authors concluded that FDG PET/CT may help distinguish actual recurrent tumor from inflammation, hemorrhage, or fibrous changes and thereby avoid unnecessary laparotomy.

Yen TC, et al. 2004

The prospective case series of 55 subjects examined the role of FDG PET in determining treatment options among a group of subjects with recurrent cervical cancer. FDG PET studies were used in addition to several clinical factors (including symptoms of recurrence, serological studies, and type of primary treatment) to determine whether salvage therapy or palliation would be appropriate. FDG PET results modified the treatment plan from radical surgery for cure to palliation in 27/55 subjects. In addition, the study examined the relative diagnostic performance of FDG PET and MRI/CT, with histopathologic examination or clinical outcome as the comparison standard. FDG PET sensitivity to detect metastatic lesions was significantly higher than that of MRI/CT (89.2% vs. 39.2%, $p < .0001$), but the sensitivities of the two methods were similar for detection of local lesions (90.0% vs. 80.0%, $p = 0.472$) (comparisons on a per-lesion basis).

The authors concluded that FDG PET benefits decisions about subsequent therapy by selecting appropriate cases of recurrent cervical cancer for salvage therapy.

3*. Is the evidence adequate to conclude that the results of a FDG PET scan will meaningfully alter recommended subsequent treatment strategy in beneficiaries who have completed an initial treatment regimen for a solid tumor and who have no signs or symptoms of tumor spread or recurrence?*

None of evidence reviewed evaluated the use of FDG PET for surveillance.

In their public comment, the requestors noted there were no well-accepted data showing a link between surveillance and improved health outcomes.

4. MEDCAC

A Medicare Evidence Development and Coverage Advisory Committee (MEDCAC) meeting was convened on this issue on August 20, 2008. Details are available at the following URL: https://www.cms.hhs.gov/mcd/viewmcac.asp?where=index&mid=44.

The Medical Evidence Development and Coverage Advisory Committee (MEDCAC) met to discuss the evidence, hear presentations and public comments, and make recommendations concerning the oncologic indications of FDG PET for nine cancers: brain, cervical, small cell lung, ovarian, pancreatic, testicular, prostate, bladder and kidney. After a presentation of the technology assessment by UA-EPC and several other presentations, the MEDCAC members voted using a numeric scale from 1 to 5, with 1 indicating no confidence and 5 indicating high confidence. The following indicates the average vote from MEDCAC members voting for each aspect. The results included:

The committee was asked to consider the following questions.

1. How confident are you that the evidence is adequate to conclude that FDG PET imaging improves physician decision making when used for the following indications for each in these nine cancers?

For Diagnosis: MEDCAC members indicated relatively stronger confidence in FDG PET effect on physician decision making in the diagnosis of ovary and pancreas neoplasms (3.0 and 2.75 respectively). MEDCAC members expressed decreased confidence in FDG PET effect on physician decision making in the diagnosis of bladder, cervix, prostate and testis neoplasms (all at 1.5).

For Staging: MEDCAC members indicated relatively stronger confidence in FDG PET effect on physician decision making in staging of cervix, ovary, and pancreas neoplasms (3.5, 3.5 and 3.25 respectively). MEDCAC members expressed relatively lower confidence in FDG PET effect on physician decision making in staging of bladder, prostate and testis neoplasms (all at 1.5).

For Restaging: MEDCAC members indicated relatively stronger confidence in FDG PET effect on physician decision making in restaging of cervix and ovary neoplasms (both at 3.5). MEDCAC members expressed relatively lower confidence in FDG PET effect on physician decision making in the restaging of bladder, testis and prostate neoplasms (1.5, 1.5 and 1.75 respectively).

For Monitoring: MEDCAC members indicated relatively stronger confidence in FDG PET effect on physician decision making in monitoring of cervix and ovary neoplasms (both at 3.5). MEDCAC members expressed relatively lower confidence in FDG PET effect on physician decision making in monitoring of testis and prostate neoplasms (1.5 and 1.75 respectively).

2. How confident are you that the evidence is adequate to conclude that FDG PET imaging improves patient oriented clinical outcomes when used for the following indications in each of these nine cancers?

For Diagnosis: MEDCAC members indicated relatively stronger confidence in FDG PET performance for diagnosis of ovary, pancreas and kidney neoplasms (3.25, 3.25 and 2.75 respectively). MEDCAC members expressed decreased confidence in FDG PET performance for diagnosis of cervix, testis and prostate neoplasms (1.5, 1.5 and 1.75 respectively).

For Staging: MEDCAC members indicated relatively stronger confidence in FDG PET performance for staging of cervix, ovary and pancreas neoplasms (3.75, 3.5 and 3.5 respectively). MEDCAC members expressed relatively lower confidence in FDG PET performance for staging of testis and brain neoplasms (1.5 and 1.67 respectively).

For Restaging: MEDCAC members indicated relatively stronger confidence in FDG PET performance for restaging of cervix and ovary neoplasms (both at 4.25). MEDCAC members expressed relatively lower confidence in FDG PET performance for restaging of testis neoplasms (1.75).

For Monitoring: MEDCAC members indicated relatively stronger confidence in FDG PET performance for monitoring of cervix, ovary and kidney neoplasms (4.0, 3.75 and 3.5 respectively). MEDCAC members expressed relatively lower confidence in FDG PET performance for monitoring of testis neoplasms (1.75).

In addition, MEDCAC members also addressed three other issues:

1. In response to the question: How confident are you that these conclusions are generalizable to other cancers, the average of voting MEDCAC members' responses was 3, ranging from 1 to 5.
2. In response to the question: How confident are you that these conclusions are generalizable to non-research FDG PET facilities in the general community, the average of voting MEDCAC members' responses was 3.25, ranging from 3 to 4.
3. In response to the question: How confident are you that these conclusions are generalizable to the Medicare beneficiary population, the average of voting MEDCAC members' responses was 4, ranging from 4 to 5.

5. Evidence-based guidelines

We did not locate nor were we provided any guidelines for the use of FDG PET imaging in cancer patients.

6. Professional Society Position Statements

We have not identified professional society position statements.

7. Expert Opinion

We did not solicit any expert opinions on the use of FDG PET for brain, cervical, ovarian, pancreatic, small cell lung and testicular cancers specifically. In that prostate cancer is the most frequent indication for FDG PET imaging in NOPR, we solicited expert opinion from Howard Scher, MD, Chief, Genitourinary Oncology Service, Memorial Sloan-Kettering Cancer Center on the usefulness of FDG PET in the management of prostate cancer. Included in this opinion were recommendations for use of FDG PET in prostate cancer for several clinical circumstances. These are:

- To identify systemic and/or local disease recurrence in a patient with a rising prostate-specific antigen (PSA) after surgery or radiation therapy as primary treatment;
- To identify and follow sites of tumor regrowth in patients who have failed hormonal therapy; and
- To provide an early readout of the effects of therapy on tumor growth.

Dr. Scher's opinion appears among others at the CMS webpage (alphabetically listed):
http://www.cms.hhs.gov/mcd/viewpubliccomments.asp?nca_id=218&rangebegin=09_16_2008&rangeend=10_17_2008#0916200810172008S

In addition, we asked the requestors to opine specifically on the topic of tumor FDG-avidity and whether or not that factor is helpful in predicting the usefulness of FDG PET for any particular indication. They made the following points:

- Glucose uptake depends upon degree of differentiation for all tumors. Some tumors e.g., well-differentiated hepatoma do not have uptake above background.

- All tumors [they] know about have some sufficiently aggressive forms that have high FDG uptake – as in the example of hormone-refractory prostate cancer.
- The presence or absence of FDG uptake in itself can be very clinically relevant. For example, presence or absence of FDG uptake is currently very important in the decision to pursue further treatment for iodine-refractory thyroid cancer, based upon data showing poor survival with FDG-avid forms of the disease and excellent survival for FDG-negative disease.
- Increased glycolytic metabolism is a fundamental property of cancer cells, and thus there is really not any cancer that is not FDG-avid. However, in general, low-grade tumors that grow more slowly tend to be less FDG avid than do their higher grade counterparts within a given tumor cell type. Examples where this has been demonstrated included low-grade sarcomas, lymphomas, and gliomas.
- Another general principle relates to those tumors that have large amounts of non-cellular stroma, such as mucinous carcinomas and desmoplastic tumors tend to be less FDG-avid; this is simply a function of partial volume averaging at the microscopic level. Commonly cited examples of tumors that are less FDG-avid than many other tumors are prostate cancer, thyroid cancer, hepatocellular carcinoma, and neuroendocrine tumors.
- Again, as a general rule, the less well differentiated all of these tumors are, the more likely they will be quite FDG-avid. In the case of prostate cancer, this typically corresponds with the onset of hormone-refractory disease. With thyroid cancer and neuroendocrine tumors, their FDG-avidity typically corresponds with their loss of endocrine-functional differentiation (so that they no longer accumulate I-131 or no longer express somatostatin receptors).
- There is apparently no current consensus standard that could be used to define FDG avidity via any *in vitro* or *in vivo* assay. A working definition of non-FDG-avid might be those cases where tumors that are large enough to be detected by FDG PET instrumentation do not have uptake above background, and are therefore not seen. A good example is Grade I hepatoma, which has SUVs ~ 2, as does normal liver.

8. Public Comments

Initial Comment Period: April 10, 2008 through May 10, 2008

CMS received 629 public comments during the first public comment period. All but one of the comments supported coverage of FDG PET for the requested indications. Eighty-five percent of the public comments were form letters expressing that support. Comments were received from medical and surgical oncologists, nuclear medicine physicians, general radiologists, other physicians, FDG PET facilities, industry associations and other sources. Any articles submitted with these public comments were not unique to those submitted by the requestor or identified by CMS during its literature review.

Second Period: September 16, 2008 through October 17, 2008

CMS received 104 public comments during the second comment period. Eighty percent of those comments were form letters from South Florida physicians expressing their support.

CMS received a comment by the requestors jointly signed by senior management of the National Oncologic FDG PET Registry (NOPR), the American College of Radiology (ACR), the American Society for Therapeutic Radiology and Oncology (ASTRO), the Academy of Molecular Imaging (AMI) and the Society of Nuclear Medicine (SNM).

In summary, three requestors comment that they believe there is strong empirical evidence to support an omnibus cancer framework that would provide coverage of FDG PET across all oncologic indications for diagnosis, staging, and restaging, including detection of suspected recurrence. The requestors also comment that they do not believe there is sufficiently mature evidence from NOPR to recommend an end the CED for the coverage of treatment monitoring at this time. The requestors propose to continue using NOPR to collect data on the value of FDG PET for treatment monitoring.

CMS received five comments from imaging industry associations favoring coverage to include the requested indications. Among the industry association comments, US Oncology commented, in part, that CMS could integrate measures for FDG PET imaging efficiency into the Physician Quality Reporting Initiative (PQRI). This issue is beyond the scope of the current national coverage analysis.

Three comments from health insurance plans criticized the available evidence and did not support coverage of the requested indications.

Additional comments of support for broader coverage came from medical and surgical oncologists, nuclear medicine physicians, general radiologists and other physicians. FDG PET facility staff, two foundations and those with unknown affiliations also submitted supportive comments.

Two comments addressed positron emission mammography (PEM). One comment addressed proton beam therapy. Neither of these topics is a component of this reconsideration request.

VIII. CMS Analysis

National coverage determinations (NCDs) are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally by Medicare (§1869(f)(1)(B) of the Act). In order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B, and must not be otherwise excluded from coverage. Moreover, with limited exceptions the expenses incurred for items or services must be "reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member." See §1862(a)(1)(A)of the Act. This section presents the agency's evaluation of the evidence considered and conclusions reached for the assessment

The Medicare regulations at 42 CFR 410.32(a) state in part, that "…diagnostic tests must be ordered by the physician who is treating the beneficiary, that is, the physician who furnishes a consultation or treats a beneficiary for a specific medical problem and who uses the results in the management of the beneficiary's specific medical problem."

We considered the evidence in the hierarchical framework of Fryback and Thornbury (1991) where Level 2 addresses diagnostic accuracy, sensitivity, and specificity of the test; Level 3 focuses on whether the information produces change in the physician's diagnostic thinking; Level 4 concerns the effect on the patient management plan and Level 5 measures the effect of the diagnostic information on patient outcomes. Most studies have focused on test characteristics and changes in physician diagnostic thinking and have not considered health outcomes, such as mortality or morbidity. We believe that health outcomes are more important than test characteristics.

As a diagnostic test, the FDG PET scan would not be expected to directly change health outcomes, i.e. there is no evidence that administration of FDG is therapeutic. Rather, a diagnostic test affects health outcomes through changes in disease management brought about by physician actions taken in response to test results. Such actions may include decisions to treat or withhold treatment, to choose one treatment modality over another, or to choose a different dose or duration of the same treatment. To some extent the usefulness of a test result is constrained by the available management alternatives.

In evaluating diagnostic tests, Mol and colleagues (2003) reported: "Whether or not patients are better off from undergoing a diagnostic test will depend on how test information is used to guide subsequent decisions on starting, stopping or modifying treatment. Consequently, the practical value of a diagnostic test can only be assessed by taking into account subsequent health outcomes." When a proven, well established association or pathway is available, intermediate health outcomes may also be considered. For example, if a particular diagnostic test result can be shown to change patient management and other evidence has demonstrated that those patient management changes improve health outcomes, then those separate sources of evidence may be sufficient to demonstrate positive health outcomes from the diagnostic test.

Questions

1. Is the evidence adequate to conclude that the results of an FDG PET scan will meaningfully alter the recommended initial treatment strategy for beneficiaries who have solid tumors or lesions suspected to be solid tumors?

2. Is the evidence adequate to conclude that the results of an FDG PET scan will meaningfully alter recommended subsequent treatment strategy in beneficiaries who have completed an initial treatment regimen for a solid tumor but who have signs or symptoms of tumor spread or recurrence?

3. Is the evidence adequate to conclude that the results of an FDG PET scan will meaningfully alter recommended subsequent treatment strategy in beneficiaries who have completed an initial treatment regimen for a solid tumor and who have no signs or symptoms of tumor spread or recurrence?

Analysis

Coverage Framework

We have received public input indicating that the current coverage framework which required cancer by cancer consideration of diagnosis, staging, restaging and monitoring response to treatment is challenging for a variety of reasons. They commented that it was burdensome to implement and was not consistent with the cancer treatment community's approach to cancer management. While that coverage framework was useful when introduced, we do not believe that it currently represents how physicians determine treatment for cancer patients. The treating physician's dilemma is to determine how to initially treat the tumor and then, based on response, develop a subsequent strategy.

The core purpose of oncologic FDG PET imaging is to identify lesions that, based on their uptake of FDG, are more likely or less likely to represent active tumor tissue. This information would be used, for example, to determine the extent of tumor spread, particularly whether or not the patient is an appropriate candidate for a definitive cure. Accurate information on the extent of the cancer may prompt the treating physician to recommend palliative treatment that may be better tolerated by the patient.

As the technical capabilities of diagnostic imaging have improved over time, physicians' use of imaging has evolved. When a patient is being evaluated for signs and symptoms that reasonably indicate the presence of a solid tumor, information on the extent and anatomic location of disease can inform the diagnosis itself. Some tumors consistently spread via hematogenous or lymphatic pathways or by local progression. Some tumors metastasize to characteristic distant anatomic locations, e.g. the liver, lungs or the spinal skeleton. This information informs both the diagnosis and the staging of the tumor. We do not believe that it is generally practical to try to apportion a single imaging study to its multiple subsidiary uses. We are unaware of any algorithm that would, for example, say that a single FDG PET study was 60 percent for diagnosis and 40 percent for staging.

This is consistent with the National Comprehensive Cancer Network (NCCN) guidelines which provide guidance to oncologists for the approach to initial and later treatment of solid malignant tumors. These guidelines (available at www.nccn.org) reflect the complex nature of cancer and explicitly call for individualization to the patient's situation and needs. We believe the guidelines offer a more directive approach for initial cancer treatment, recognizing a greater level of evidence for this. They provide more options and less direction for dealing with heterogenous clinical situations encountered in patients with recurrent solid malignancies. CMS believes the revised coverage framework for oncologic uses of FDG PET reflects this fundamental dichotomy between the initial assessment and treatment planning of a solid tumor and subsequent assessment and treatment planning in the face of tumor recurrence.

Stakeholders have also noted that oncologic staging is a one-way-street, i.e. once assigned, tumor stage cannot be changed. Thus, the concept of restaging, while understandable in the context of determining ongoing tumor burden, has posed challenges. We have also been informed that restaging and monitoring response to therapy may be difficult to distinguish on a practical basis, i.e. the detection of residual tumor burden will provide information on the anatomic location of distal spread but at the same time indicate how well the patient has responded to the prior therapy.

Therefore, we are proposing a simpler framework for our coverage policies regarding the uses of FDG PET. This proposed framework divides oncologic uses of FDG PET into two distinct parts:

- Determination by the treating physician of the initial treatment strategy, and.
- Assessment of the success of the initial treatment strategy to determine the need for and content of a subsequent treatment strategy.

The uses of FDG PET that were previously characterized as diagnosis and staging have been brought into the first part, as these clearly relate to the development of the initial treatment strategy. The uses of FDG PET that were previously characterized as restaging and monitoring response to treatment have been brought into the second part, as these clearly come after the initial treatment strategy. All current NCDs that address coverage of FDG PET imaging for oncologic conditions would be transitioned into this new framework. Coverage within this new framework is discussed below.

Separately, we know from clinical practice experience that patients are often confused by the terminology describing the anatomic location of a tumor and the histopathologic classification of a tumor. For example, cancerous tissue found in the lung may arise from a primary lung cancer, e.g. squamous carcinoma of the lung. Cancerous tissue found in the lung may also arise from metastases from other anatomic sites, e.g. the breast or the kidney. In essence, some cancers found in the lung are not lung cancer. Similar analogies can be made for other anatomic locations such as the liver, brain, and bones, which are frequent sites of metastatic spread. Our point here is that the identification of a suspicious lesion in the lung does not always result in a diagnosis of lung cancer, even if the lesion is cancerous. In our current NCD, we separately consider lung cancer and solitary pulmonary nodules. In light of this new framework, there is no longer a need to separately discuss the characterization of a solitary pulmonary nodule outside of the work-up for a possible lung cancer, and we propose to remove that distinction.

Summary of Evidence

As discussed in the 2005 NCA, we determined that FDG PET scans were no longer experimental, but at that time we believed the evidence was insufficient to reach a conclusion that FDG PET was broadly reasonable and necessary, though there was a sufficient inference of benefit drawn to support limited coverage if certain safeguards for patients were provided. This inference was based on both the pathophysiologic basis for FDG PET's usefulness in cancer, as well as the positive coverage in several cancers for which there is sufficient evidence to warrant coverage. As we also noted in 2005, we believed this to be a unique instance where general knowledge of a technology is well accepted. Now, however, in some instances, the specific applications are better determined. In the current reconsideration, we are reviewing the evidence of FDG PET in the context of our proposed new coverage framework.

1. Is the evidence adequate to conclude that the results of an FDG PET scan will meaningfully alter the recommended initial treatment strategy for beneficiaries who have solid tumors or lesions suspected to be solid tumors?

With the publication of results derived from NOPR and the advances in the current evidence base, which consistently note the physicians' use of FDG PET imaging results to guide management for several cancer indications, we believe that we have sufficient evidence to propose broad FDG PET coverage for use in solid tumors in the context of initial treatment strategy. Specifically, we believe that FDG PET results are used by treating physicians to discriminate localized from widespread disease and to identify lesions that are appropriate for biopsy.

In general, the literature is consistent in finding FDG PET useful for initial treatment strategy in patients with both biopsy proven cancer and in patients with suspected tumor burden. Although most (except for NOPR) were case series and some were studies of fewer than 40 people (Suzuki, et al. 2007 , Ng SH, et al. 2004), there were appropriate comparators (histopathology) to FDG PET and the conclusions were consistent across most of the evidence presented in the evidence section and the appendix of studies.

We believe there is adequate evidence that FDG PET changes the physician-recommended treatment strategy, especially as related to surgical and possibly curative strategies. As presented in the evidence section, authors note that: "When considering the overall patient population of our study, the most meaningful result was that…the majority would have been shifted to possible surgical treatment after FDG PET. This is important as a therapeutic option with curative intent administered as soon as possible, without awaiting evolution to malignancy in the case of indeterminate nodules, will certainly lead to the best achievable clinical outcome (Pepe 2005)." In addition, the TA (McEwan, et al. 2008) notes that there was evidence of the utility of FDG PET for diagnosing, staging, or detecting recurrences, all of which affect treatment strategy.

In our current NCD, coverages for two cancers—breast and melanoma—do not easily fit this new framework. For breast cancer, we noncover diagnosis of breast cancer and staging of axillary nodes. We cover staging of distant metastasis. Since we did not review specific evidence on breast cancer, we will maintain that coverage and make appropriate annotations in that regard in our revised NCD.

Similarly, for melanoma, we cover FDG PET for diagnosis and staging but we explicitly noncover FDG PET for evaluation of regional lymph nodes. We will maintain that coverage also.

However, we do solicit public comment on the potential of modifying these exceptions to the coverage for initial treatment strategy if there is evidence in support of that.

As part of this analysis, we did review new evidence on the use of FDG PET imaging for prostate cancer. We believe the evidence does not demonstrate that it is useful for the initial treatment strategy in that it does not alter patient management or improve health outcomes. Expert opinion generally agreed with this. Therefore, we are also proposing noncoverage of FDG PET in the initial management of prostate cancer

2. Is the evidence adequate to conclude that the results of an FDG PET scan will meaningfully alter recommended subsequent treatment strategy in beneficiaries who have completed an initial treatment regimen for a solid tumor but who have signs or symptoms of tumor spread or recurrence?

In this decision, we reviewed new evidence on the use of FDG PET imaging in the subsequent treatment strategy of solid tumors with the exception of breast, cervix, colorectal, esophagus, head and neck (non-CNS/thyroid), lymphoma, melanoma, non-small cell lung, and thyroid.

The need for additional evidence on the use of FDG PET to guide subsequent treatment strategy in this group is indicated by the internal technology assessment. The literature reviewed by CMS was promising, but had some limitations. In some studies (Connell CA, et al. (2007), Chung, et al. 2007) histopathologic confirmation was not obtained in all samples, thus making it difficult to determine the true test performance of FDG PET for use in subsequent treatment strategy. In addition to a much smaller literature base from which to draw conclusions about the use of FDG PET to guide subsequent treatment strategy, the size of the studies was also small (Pepe, et al 2005 n = 20; Connell CA, et al. 2007 n=30). As noted previously, there continues to be some difficulty in distinguishing between inflammation (especially post-surgical) and malignancy when FDG PET is used alone and not in concert with other modalities (Votrubova J, et al. 2006).

Data from prospective clinical studies can inform the subsequent care provided to patients, and the NOPR has contributed to this effort. We believe that there is a need for more prospective data to answer the question of use of FDG PET for monitoring response to treatment and subsequent treatment strategy. The requestors have stated that continuation of NOPR in its present form will not provide information beyond what has already been derived from it. However, they do recommend that evidence development continue for the monitoring indication in the current framework. This is consistent with the external technology assessment (McEwan, et al. 2008) conclusions that called for "additional studies … to augment the evidence base…and reach firm conclusions." (McEwan, et al 2008):

Although FDG PET technology development appears to have reached maturity with the fusion of 18FDG PET and CT in an integrated system, imaging protocols will continue to be refined over the next few years. Further evaluations of the utility of this technology should be done with developments concentrating on enhancing patient throughput and establishing new and more focused clinical applications in various subpopulations of patients.

…some of the most important roles of 18FDG PET and 18FDG PET/CT have not been sufficiently explored (e.g., estimating prognosis…changing treatment modalities). If the total clinical contributions of 18FDG PET and 18FDG PET/CT have to be evaluated to inform policy decisions, these information gaps need to be filled with new methodological approaches.

Given the limitations of the medical literature reviewed for this indication—it is much less robust than that for initial treatment strategy—and, given the findings of the external technology assessment stated previously, CMS finds the use of FDG PET promising but not complete for guiding subsequent treatment strategy for the tumor types not currently covered. Therefore, we propose that FDG PET for the determination of subsequent treatment strategy for tumor types other than breast, cervix, colorectal, esophagus, head and neck (non-CNS/thyroid), lymphoma, melanoma, non-small cell lung, and thyroid is not reasonable and necessary under 1862(a)(1)(A). However, we do believe that FDG PET imaging for subsequent therapy for this group is reasonable and necessary under 1862(a)(1)(E)—our CED policy.

Under the authority of § 1862(a)(1)(E), coverage with evidence development/coverage with study participation (CED/CSP) will allow Medicare to cover certain items or services for which the evidence is not adequate to support coverage under §1862(a)(1)(A) and where additional data gathered in the context of clinical care would further clarify the impact of these items and services on the health of Medicare beneficiaries. CSP allows CMS to determine that an item or service is only reasonable and necessary when it is provided within a research setting where there are added safety, patient protections, monitoring, and clinical expertise. Under section 1142, research may be conducted on the outcomes, effectiveness, and appropriateness of health care services and procedures to identify the manner in which diseases, disorders, and other health conditions can be prevented, diagnosed, treated, and managed clinically.

To qualify for reimbursement, such a study must be designed to produce evidence that could be used in a future national coverage decision that would focus on whether the item or service should be covered by Medicare under §1862(a)(1)(A). Payment for the items and services provided in the study will be restricted to the Medicare qualified patients involved as human subjects in the study.

Ideally, this study would be designed to collect additional information at the time of the scan to assist in patient management. This study would examine valid, measurable outcomes when possible and avoid measuring intermediate outcomes. Changes in management that avoid unnecessary biopsy, invasive surgery or dangerous chemotherapeutic agents would be beneficial for patients. Outcomes that show significant changes in management with the use of FDG PET scans would improve the evidence in this arena.

We believe that a limited amount of additional evidence can conclusively address our concerns, as the outcomes of greatest interest are discrete events that are readily identified. These include

- surgical procedures, including biopsies,
- anticancer chemotherapy,
- radiotherapy,
- hospitalization and
- mortality.

We believe that prospective clinical studies are required to assure that any differences in outcomes are confidently attributable to the additional information provided by FDG PET rather than to bias or other factors. Furthermore, enrolled subjects must adequately represent the Medicare beneficiary population. If these or other studies produce sufficient evidence for us to confidently conclude that such uses of FDG PET that are covered under 1862(a)(1)(E) can be covered under 1862(a)(1)(A), we anticipate reconsidering this NCD to make such changes as are appropriate.

We therefore propose that FDG PET to assess response to the initial antitumor treatment strategy and guide decisions on subsequent treatment strategies for tumor types other than breast, cervix, colorectal, esophagus, head and neck (non-CNS/thyroid), lymphoma, melanoma, non-small cell lung, and thyroid is reasonable and necessary only under 1862(a)(1)(E) Coverage with Evidence Development, specifically Coverage with Study Participation (CSP).

We have consulted with AHRQ who has agreed that the study questions and requirements outlined above are consistent with section 1142 of the Social Security Act.

3. Is the evidence adequate to conclude that the results of an FDG PET scan will meaningfully alter recommended subsequent treatment strategy in beneficiaries who have completed an initial treatment regimen for a solid tumor and who have no signs or symptoms of tumor spread or recurrence?

CMS notes that there is a paucity of evidence in the literature regarding the role of FDG PET for this use. In their public comment, requestors noted there was no well-accepted data showing that monitoring is linked to improved health outcomes. Hence, we believe that such uses should generally be covered only under CSP.

We remind the reader that Question 3 is posed in the context of a patient who has a known diagnosis of a solid tumor and in whom his treating physician is still actively managing the treatment of the solid tumor. We are not considering the use of PET as a screening test rather than as a diagnostic test.

Additionally, we note the paucity of any national, consensus guidelines on when FDG PET should be used in the management of solid tumors. Even the requestors have found instances where physicians were ordering FDG PET scans when there was little if any likelihood that the results would provide useful information. We believe that there is a pressing need for the oncology imaging community to create evidence-based guidelines for the use of FDG PET in 2009. CMS will look forward to reviewing these guidelines when they become public and, if necessary, re-opening the FDG PET decision in order to accommodate these evidence-based guidelines as necessary for the appropriate use of FDG PET in cancer management.

IX. Conclusion

CMS was asked to reconsider Section 220.6 of the National Coverage Determinations Manual to end the prospective data collection requirements across all oncologic indications of FDG PET except for monitoring response to treatment. Section 220.6 of the NCD Manual establishes the requirement for prospective data collection for FDG PET used in the diagnosis, staging, restaging and monitoring response to treatment for brain, cervical, ovarian, pancreatic, small cell lung and testicular cancers, as well as for cancer indications not previously specified in Section 220.6 in its entirety.

We received public input indicating that the current coverage framework which required cancer-by-cancer consideration of diagnosis, staging, restaging and monitoring response to treatment should be replaced by a more omnibus consideration. Thus, we broadened the scope of this review through an announcement on our website and solicited additional public comment on the use of FDG PET imaging for solid tumors so that we could transparently consider this possibility. Therefore, we propose the following decision, which would replace sections 220.6.2, 220.6.3, 220.6.4, 220.6.5, 220.6.6, 220.6.7, 220.6.11, 220.6.12, 220.6.14 and 220.6.15 of the NCD Manual.

1. Framework
We propose a new coverage framework that would replace the four-part diagnosis, staging, restaging and monitoring response to treatment categories with a two-part framework that differentiates FDG PET imaging used to inform the initial treatment strategy from other uses related to guiding subsequent treatment strategies after the completion of initial treatment. We propose to make this change for all NCDs that address coverage of FDG PET for oncologic conditions.

2. Initial Treatment Strategy
CMS proposes that the evidence is adequate to determine that the results of FDG PET imaging are useful in determining the appropriate initial treatment strategy for beneficiaries with suspected solid tumors and thus improve health outcomes and are reasonable and necessary under §1862(a)(1)(A) of the Social Security Act.

Therefore, CMS will cover one FDG PET study for beneficiaries who have solid tumors that are biopsy proven or strongly suspected based on other diagnostic testing when the beneficiary's treating physician determines that the FDG PET study is needed to determine the location and/or extent of the tumor for the following therapeutic purposes related to the initial treatment strategy:

- To determine whether or not the beneficiary is an appropriate candidate for an invasive diagnostic or therapeutic procedure; or

- To determine the optimal anatomic location for an invasive procedure; or
- To determine the anatomic extent of tumor when the recommended anti-tumor treatment reasonably depends on the extent of the tumor.

As an exception to this decision:

a. CMS has reviewed evidence on the use of FDG PET imaging to determine initial antitumor treatment in patients with adenocarcinoma of the prostate. CMS proposes that the available evidence does not demonstrate that FDG PET imaging improves physician decision making in the determination of initial anti-tumor treatment strategy in Medicare beneficiaries who have adenocarcinoma of the prostate, does not improve health outcomes and is thus not reasonable and necessary under §1862(a)(1)(A) of the Social Security Act. Therefore we are proposing that FDG PET is nationally noncovered for this indication.
b. CMS did not review new evidence on the use of FDG PET imaging to determine initial antitumor treatment in breast cancer; thus we are not proposing any change to the current coverage policy for FDG PET in breast cancer. We will continue to cover FDG PET imaging for the initial treatment strategy for male and female breast cancer only when used in staging distant metastasis. FDG PET imaging for diagnosis and initial staging of axillary nodes will remain noncovered.
c. CMS did not review new evidence on the use of FDG PET imaging of regional lymph nodes in melanoma; thus we are not proposing any change to the current NCD for FDG PET in melanoma. CMS will continue noncoverage of FDG PET for the evaluation of regional lymph nodes in melanoma. Other uses to determine initial treatment strategy remain covered.

3. Subsequent Treatment Strategy
CMS reviewed evidence on the use of FDG PET in the subsequent treatment strategy for patients with tumor types other than breast, cervix, colorectal, esophagus, head and neck (non-CNS/thyroid), lymphoma, melanoma, non-small cell lung, and thyroid. For all other tumor types, CMS proposes that the available evidence is not adequate to determine that FDG PET imaging improves physician decision making in the determination of subsequent anti-tumor treatment strategy and thus does not improve health outcomes in Medicare beneficiaries and is not reasonable and necessary under §1862(a)(1)(A) of the Social Security Act. However, we propose that the available evidence is sufficient to determine that FDG PET imaging for subsequent anti-tumor treatment strategy is reasonable and necessary under §1862(a)(1)(E) through Coverage with Evidence Development/Coverage with Study Participation (CED/CSP)) of the Social Security Act.

Therefore, we will cover a subsequent FDG PET study for these tumor types when the beneficiary’s treating physician determines that the FDG PET study is needed to inform the subsequent antitumor treatment strategy and the beneficiary is enrolled in, and the FDG PET provider is participating in, one of the following types of prospective clinical studies:

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- A clinical trial of FDG PET that meets the requirements of Food and Drug Administration (FDA) category B investigational device exemption (42 CFR 405.201); or
- An FDG PET clinical study that is designed to collect additional information at the time of the scan to assist in patient management. Qualifying clinical studies must ensure that specific hypotheses are addressed; appropriate data elements are collected; hospitals and providers are qualified to provide the PET scan and interpret the results; participating hospitals and providers accurately report data on all enrolled patients not included in other qualifying trials through adequate auditing mechanisms; and all patient confidentiality, privacy, and other Federal laws must be followed.

The study must adhere to the following standards of scientific integrity and relevance to the Medicare population:

a. The principal purpose of the research study is to test whether a particular intervention potentially improves the participants' health outcomes.
b. The research study is well-supported by available scientific and medical information or it is intended to clarify or establish the health outcomes of interventions already in common clinical use.
c. The research study does not unjustifiably duplicate existing studies.
d. The research study design is appropriate to answer the research question being asked in the study.
e. The research study is sponsored by an organization or individual capable of executing the proposed study successfully.
f. The research study is in compliance with all applicable Federal regulations concerning the protection of human subjects found in the Code of Federal Regulations (CFR) at 45 CFR Part 46. If a study is regulated by the Food and Drug Administration (FDA), it also must be in compliance with 21 CFR Parts 50 and 56.
g. All aspects of the research study are conducted according to the appropriate standards of scientific integrity.
h. The research study has a written protocol that clearly addresses, or incorporates by reference, the Medicare standards.
i. The clinical research study is not designed to exclusively test toxicity or disease pathophysiology in healthy individuals. Trials of all medical technologies measuring therapeutic outcomes as one of the objectives meet this standard only if the disease or condition being studied is life-threatening as defined in 21 CFR § 312.81(a) and the patient has no other viable treatment options.
j. The clinical research study is registered on the www.ClinicalTrials.gov website by the principal sponsor/investigator prior to the enrollment of the first study subject.
k. The research study protocol specifies the method and timing of public release of all pre-specified outcomes to be measured including release of outcomes if outcomes are negative or study is terminated early. The results must be made public within 24 months of the end of data collection. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. However, a full report of the outcomes must be made public no later than three (3) years after the end of data collection.
l. The research study protocol must explicitly discuss subpopulations affected by the treatment under investigation, particularly traditionally underrepresented groups in clinical studies, how the inclusion and exclusion criteria affect enrollment of these populations, and a plan for the retention and reporting of said populations on the trial. If the inclusion and exclusion criteria are expected to have a negative effect on the recruitment or retention of underrepresented populations, the protocol must discuss why these criteria are necessary.
m. The research study protocol explicitly discusses how the results are or are not expected to be generalizable to the Medicare population to infer whether Medicare patients may benefit from the intervention. Separate discussions in the protocol may be necessary for populations eligible for Medicare due to age, disability or Medicaid eligibility.

Consistent with section 1142 of the Social Security Act (the Act), the Agency for Healthcare Research and Quality (AHRQ) supports clinical research studies that the Centers for Medicare and Medicaid Services (CMS) determines meet the above-listed standards and address the above-listed research questions.

For the nine tumor types listed below, we will continue to cover FDG PET for those indications currently covered under § 1862(a)(1)(A). We have not reviewed new evidence on these nine indications since they were reviewed in prior NCDs and we have not received public input suggesting coverage for these uses should be restricted. These include:

- Breast
- Cervix
- Colorectal
- Esophagus
- Head and Neck (non-CNS/thyroid)
- Lymphoma
- Melanoma
- Non-small cell lung
- Thyroid

We do propose transitioning the current framework—diagnosis, staging, restaging and monitoring—into the initial treatment and subsequent treatment strategy framework while maintaining current coverage.

See Appendix A for a chart summarizing the effect of these changes.

We are requesting public comments on this proposed determination pursuant to section 1862(1) of the Social Security Act. We are particularly interested in comments that include new evidence we have not reviewed here or in past considerations of this NCD.

We are specifically interested in comments on the following questions:

1. Should the current framework for evaluating the use of FDG PET imaging be modified as proposed?
2. Does the evidence support the broad expansion of coverage of FDG PET imaging to all solid tumors when determining initial treatment strategy?
3. Does the evidence support the restriction of coverage of FDG PET imaging in solid tumors when determining subsequent treatment strategy to coverage with evidence development?
4. For breast cancer and melanoma that have noncoverage for initial treatment strategy, is there evidence that would support their removal from the list of exceptions to coverage for initial treatment strategy?
5. 5. For the nine cancers that have coverage for subsequent treatment strategy, is there evidence that would support restricting their coverage to CED?

After considering the public comments and any additional evidence we will make a final determination and issue a final decision memorandum.

Appendix A: Effect of Coverage Changes on Oncologic Uses of FDG PET

	Current Framework					**Proposed Framework**	
Solid Tumor Type	Diagnosis	Staging	Restaging	Monitoring		Initial Treatment *	Subsequent Treatment **

Brain	CED	CED	CED	CED	Cover	CED
					1	Cover
Breast (female and male)	N/C	1	Cover	Cover	Cover	Cover
					Cover	Cover
Cervix	CED	Cover	Cover	CED	Cover	Cover
Colorectal	Cover	Cover	Cover	CED	Cover	Cover
					Cover	Cover
Esophagus	Cover	Cover	Cover	CED	2	Cover
Head & Neck (not thyroid or CNS)	Cover	Cover	Cover	CED	Cover	Cover
					Cover	CED
Lymphoma	Cover	Cover	Cover	CED	Cover	CED
					N/C	CED
Melanoma	Cover	2	Cover	CED	Cover	CED

					Cover	CED
Non-small cell lung	Cover	Cover	Cover	CED	Cover	3
Ovary	CED	CED	CED	CED	Cover	CED
Pancreas	CED	CED	CED	CED	Cover	CED
Prostate	CED	CED	CED	CED		
Small cell lung	CED	CED	CED	CED		
Soft Tissue Sarcoma	CED	CED	CED	CED		
Thyroid	CED	CED	3	CED		
Testes	CED	CED	CED	CED		

All other solid tumors	CED	CED	CED	CED	

* Formerly “diagnosis” and “staging”
** Formerly “restaging” and “monitoring response to treatment when a change in treatment is anticipated”
N/C = noncover

(1) Breast: Covered for initial staging of metastatic disease. Noncovered for initial staging of axillary lymph nodes.
(2) Melanoma: Noncovered for initial staging of regional lymph nodes
(3) Thyroid: Covered for restaging of follicular cell types

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